Angiogenesis, cardiomyocyte proliferation and anti-fibrotic effects underlie structural preservation post-infarction by intramyocardially-injected cardiospheres.

Journal: PLoS One

Publication Year: 2014

Authors: Eleni Tseliou, Geoffrey de Couto, John Terrovitis, Baiming Sun, Liu Weixin, Linda Marban, Eduardo Marban

PubMed link: 24558402

Funding Grants: Mechanism of heart regeneration by cardiosphere-derived cells

Public Summary:
We sought to understand the cellular and tissue-level changes underlying the attenuation of adverse remodeling by cardiosphere transplantation in acute myocardial infarction (MI).

Scientific Abstract:
OBJECTIVE: We sought to understand the cellular and tissue-level changes underlying the attenuation of adverse remodeling by cardiosphere transplantation in acute myocardial infarction (MI). BACKGROUND: Cardiospheres (CSps) are heart-derived multicellular clusters rich in stemness and capable of multilineage differentiation. Post-MI CSp transplantation improves left ventricular (LV) function and attenuates remodeling in both small and large animal studies. However, the mechanisms of benefit have not yet been fully elucidated. METHODS: Four groups were studied: 1) "Sham" (Wistar Kyoto rats with thoracotomy and ligature without infarction); 2) "MI" (proximal LAD ligation with peri-infarct injection of vehicle); 3) "MI+CSp" (MI with cardiospheres injected in the peri-infarct area); 4) "Small MI" (mid-LAD ligation only). RESULTS: In vivo 1 week after CSp transplantation, LV functional improvement was associated with an increase in cardiomyocyte proliferation. By 3 weeks, microvessel formation was enhanced, while cardiomyocyte hypertrophy and regional fibrosis were attenuated. Collagen deposition was reduced, collagen degradation was enhanced, and MMPs were upregulated. The beneficial effects of CSp transplantation were not observed in the Small MI group, indicating that the effects are not solely due to CSp-induced cardioprotection. In vitro, CSp-conditioned media reduced collagen production in coculture with fibroblasts and triggered neoangiogenesis in an ex vivo aortic ring assay. CONCLUSION: Cardiospheres enhance cardiomyocyte proliferation and angiogenesis, and attenuate hypertrophy and fibrosis, in the ischemic myocardium. These synergistic effects underlie the attenuation of adverse remodeling by cardiospheres.